Antipsychotics in the Treatment of Delirium in Critically Ill Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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OBJECTIVES: To conduct a systematic review and meta-analysis assessing whether the use of antipsychotic medications in critically ill adult patients with delirium impacts patient-important outcomes.

DATA SOURCES: A medical librarian searched Ovid MEDLINE, EMBASE, APA PsycInfo, and Wiley's Cochrane Library as well as clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform up to November 2023.

STUDY SELECTION: Independently and in duplicate, reviewers screened abstracts and titles for eligibility, then full text of qualifying studies. We included parallel-group randomized controlled trials (RCTs) that included critically ill adult patients with delirium. The intervention group was required to receive antipsychotic medications at any dose, whereas the control group received usual care or placebo.

DATA EXTRACTION: Reviewers extracted data independently and in duplicate using a piloted abstraction form. Statistical analyses were conducted using RevMan software (version 5.4).

DATA SYNTHESIS: Five RCTs ($n = 1750$) met eligibility criteria. The use of antipsychotic medications compared with placebo did not increase the number of delirium- or coma-free days (mean difference 0.90 d; 95% CI, −0.32 to 2.12; moderate certainty), nor did it result in a difference in mortality, duration of mechanical ventilation, ICU, or hospital length of stay. The use of antipsychotics did not result in an increased risk of adverse events (risk ratio 1.27; 95% CI, 0.71–2.30; high certainty). Subgroup analysis of typical versus atypical antipsychotics did not identify any subgroup effect for any outcome.

CONCLUSIONS: In conclusion, our systematic review and meta-analysis demonstrated with moderate certainty that there is no difference in delirium- or coma-free days when delirious critically ill adults are treated with antipsychotic medications. Further studies in the subset of patients with hyperactive delirium may be of benefit.

KEYWORDS: antipsychotics; critical illness; delirium

Delirium is a common occurrence in critically ill patients admitted to the ICU, with the incidence occurring in approximately 50% of patients (1). Delirium is known to negatively impact both short and long-term patient outcomes (2). For instance, delirium can be distressing to patients and families alike, and has been strongly associated with a prolonged hospital stay, cognitive impairment as far as 12 months out from ICU discharge, and even increased mortality (2, 3).

A recent systematic review (4) identified that dexmedetomidine may reduce the risk of delirium in mechanically ventilated patients; however, was unable to

***See also p. 1160.**

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SHOUT
SHARE
IT

KEY POINTS

Question: In critically ill adults with delirium, does the administration of antipsychotic medications improve patient outcomes?

Findings: In this systematic review and meta-analysis, we found the scheduled administration of antipsychotic medications compared with usual treatment or placebo resulted in no difference in delirium- or coma-free days (mean difference 0.90 d; 95% CI, –0.32 to 2.12; moderate certainty), nor did it result in a difference in mortality, duration of mechanical ventilation, ICU, or hospital length of stay. The use of antipsychotics did not result in an increased risk of adverse events (risk ratio 1.27; 95% CI, 0.71– 2.30; high certainty).

Meanings: There is no difference in delirium- or coma-free days when antipsychotics are administered to critically ill patients with delirium.

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assess whether dexmedetomidine prevented or treated delirium. Likewise, there are currently no medications with substantial evidence for benefit in patients with delirium (3). Antipsychotic medications have historically been used in an effort to manage symptoms; in particular harnessing their sedating properties to aid in hyperactive, agitated patients. Current guidelines (3), however, recommend against their routine use due to a lack of demonstrated benefit.

Several systematic reviews (5–7) have been conducted examining various antipsychotics in the treatment of delirium in critically ill patients without finding evidence of meaningful benefit. These studies, however, have historically been limited to one specific antipsychotic rather than the class and included patients who were not admitted to the ICU. Although a recent systematic review (8) included the recently published AID-ICU (9) and EuRIDICE (10) trials, it focused on haloperidol as the sole intervention and included a variety of comparators including placebo, other antipsychotics, opioids, benzodiazepines, and antiemetics. Furthermore, the outcomes assessed were largely limited to mortality and serious adverse events. Considering this, we conducted a systematic review and meta-analysis to capture the updated evidence regarding the potential benefits and harms of treating ICU delirium with antipsychotics as a class.

MATERIALS AND METHODS

This study was prospectively registered PROSPERO: CRD42023397132.

Study Selection

We included parallel-group randomized controlled trials (RCTs) that included critically ill adult patients (≥ 18 yr old) with a positive screen for delirium as established by the study authors. The intervention group was required to receive antipsychotic medications at any dose, frequency, initiation time, route, or duration of treatment, whereas the control group received usual care or placebo. Eligible studies reported at least one of: delirium-/coma-free days (the main outcome of interest), ICU length of stay, duration of invasive mechanical ventilation, mortality at 28 days, mortality at longest follow-up, cognitive function/general disability score, disposition destination, use of rescue medications (i.e., benzodiazepines, propofol), or adverse events including arrhythmias, cardiac arrest, hypotension, or QTc prolongation.

Search Strategy

A literature search was performed by an information specialist following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Literature Search Extension (PRISMA-S) guidance (11), using a peer-reviewed search strategy (**Supplement Table 1**, http://links.lww.com/CCM/H511). The strategy was reviewed according to the methods described in the study by McGowan et al (12). Published literature was identified by searching the following bibliographic databases in November 2022 and updated again on November 17, 2023: Medline (1946–) with in-process records and daily updates, EMBASE (1974–), and APA PsycInfo (1806–) via Ovid, and Cochrane's CENTRAL via Wiley. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings and Key Words. The main search concepts were antipsychotic agents, delirium, and intensive care. A methodological search filter was applied to limit the retrieval of RCTs in the Ovid databases. Record retrieval was not limited by date or language, and animal-only records were removed. Duplicate records were removed between Medline, Embase, and PsycInfo using Ovid default

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duplicate detection, with any additional duplicates identified and removed in Covidence. We searched ongoing trials in clincialtrials.gov and the World Health Organization International Clinical Trials Registry Platform up to November 10, 2022, and once more to November 17, 2023 (Supplement Table 1, http://links.lww.com/CCM/H511). Finally, we screened the reference list of review articles for additional studies.

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Selection of Trials

Citations of all potentially eligible articles were screened independently and in duplicate. Reviewers first screened titles and abstracts to identify full studies for review and evaluated the full texts of eligible studies. Disagreements between reviewers were resolved through discussion, and consultation with a third reviewer when an agreement could not be reached.

Data Abstraction

In duplicate, reviewers used prepiloted abstraction forms to collect patients' demographic data, outcomes, and assess risk of bias (ROB). Disagreements were resolved through discussion until consensus was reached.

Missing Data

The authors of three eligible trials were contacted for missing or unclear data, two of which (9, 13) replied. Another author of a registered protocol was contacted to provide unpublished data; however, did not reply. Finally, a fifth author was contacted regarding incomplete data published in abstract form only; however, no further information was provided.

Risk of Bias

Two reviewers independently assessed trials for ROB using the Cochrane ROB tool 2.0. For each included trial, we judged individual outcomes as low, some concern, or high ROB in the domains of the randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, and selection of reported results. The overall ROB for each included trial was categorized as low if the ROB was low in all domains, having some concerns if there were some concerns for ROB in any domain but none deemed to be high risk, or high if the ROB was high in at least one domain. Disagreements were resolved by discussion to reach consensus.

Statistical Analysis

Statistical analyses were conducted using RevMan software (Review Manager [RevMan], version 5.4. The Cochrane Collaboration, 2020). We used the DerSimonian and Laird random-effects model (14) to pool the weighted effect of estimates across all studies. The inverse variance method was used to estimate study weights. We calculated pooled risk ratios (RR) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with a corresponding 95% CI. We planned to inspect funnel plots to assess for publication bias if more than 10 trials existed for a given outcome (15). Three studies had three trial arms (two antipsychotics and one placebo). The conversion of data where needed (i.e., from interquartile range to SD) and pooling for the antipsychotic arms of trials with multiple drugs was done in accordance with the Cochrane Handbook (16). For subgroup analyses the number of participants in the control arm was divided in two (and rounded up where it was an uneven number) in an effort to overcome unit-of-analysis error (16).

Trial Sequential Analysis

We used trial sequential analysis (TSA) software (v. 0.9.5.10 beta, Copenhagen Trial Unit, ctu.dk/tsa) to determine if the required sample size to reach the threshold for statistical significance was met to reduce the risk of spurious findings (15, 17, 18). Cumulative *z*-scores (19) were constructed. If the cumulative *z*-curve crossed the threshold, which we assumed to be a mean difference of 2 days for delirium-free days and relative risk reduction of 15% for mortality, we would conclude that a sufficient level of evidence for the intervention effect has been reached and no further trials are necessary (19). If the cumulative *z*-curve did not cross the threshold boundaries, we concluded that the quantity of evidence was insufficient to rule out a type 1 error (19). We conducted TSA to maintain a risk of 5% for type 1 error and a power of 80%.

Heterogeneity and Subgroup Analysis

Statistical heterogeneity was assessed using the Chi-square and I^2 statistics. A Chi-square value of less than 0.1 or an I^2 value of greater than 50% qualified as

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significant heterogeneity (20). Heterogeneity between studies was explored by performing predefined subgroup analyses to investigate whether certain baseline factors modified treatment effects. These subgroups included: typical versus atypical antipsychotics, active versus hypoactive delirium, and comparator agents. Given the adoption of multicomponent strategies with evidence to support their positive impact on and improved detection of delirium in recent years, a post hoc subgroup analysis was conducted to assess differences in treatment effect in studies conducted before and after these interventions (set at the year 2018).

Meta-Regression

We intended to perform meta-regression by age and dose of antipsychotic medication (if able to based on size of data).

Sensitivity Analysis

Sensitivity analysis was planned to explore the impact on the pooled results by removing high ROB studies and studies with concern for ROB. We hypothesized that the treatment effect would be smaller after excluding high ROB studies. We also planned to perform a sensitivity analysis excluding abstracts (although we did not anticipate any difference).

Assessing the Quality of Evidence

Two reviewers independently and in duplicate applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (21) to assess the quality of evidence for each outcome. We used the GRADEpro software (GRADEpro GDT: GRADEpro Guideline Development Tool [Software], McMaster University, 2020) (22) to create the evidence profile. Summary of findings table for the assessment of the certainty of evidence for each outcome is available in **Supplement Table 2** (http://links.lww.com/CCM/H511).

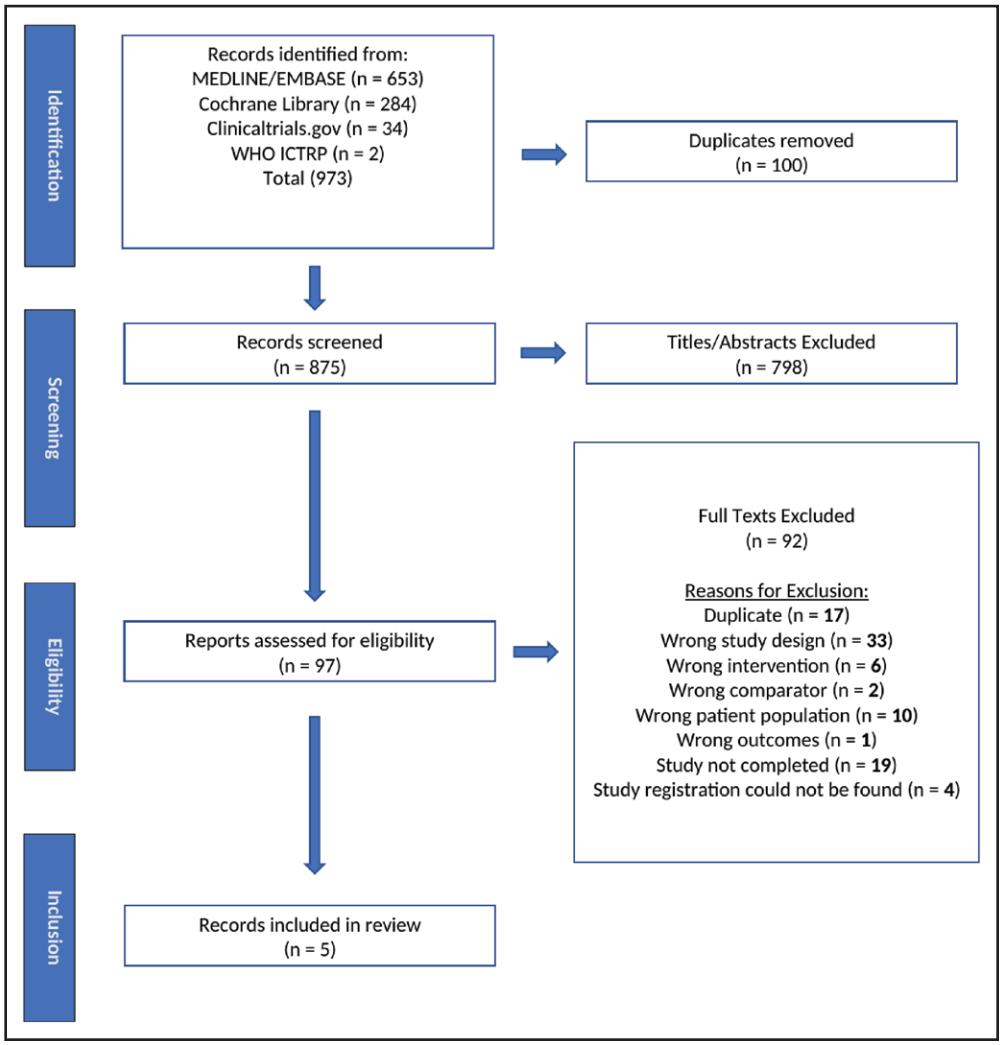

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart. WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

RESULTS

Screening

Our electronic search identified 975 citations (**Fig. 1**) of which 875 remained after removal of duplicates. Title and abstract screening resulted in 97 studies undergoing full-text review, of which 92 were excluded (**Supplement Table 3**, http://links.lww.com/CCM/H511). Five studies met eligibility criteria and were included in the final quantitative analysis.

Characteristics of Included Studies

There was a total of 1750 patients included in the

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five eligible trials (9, 10, 23–25) (**Supplement Table 4**, http://links.lww.com/CCM/H511). All five studies used the Confusion Assessment Method for the ICU or Intensive Care Delirium Screening Checklist as delirium screening tool. The mean age was 65.8 ± 13.0 (SD) years and 38% of enrolled patients were female. In those that reported it (23–25), the mean Acute Physiologic Assessment and Chronic Health Evaluation II score was 28.07 ± 7.90. Thirty-three percent of patients had hyperactive delirium, whereas the remaining 67% were hypoactive. The intervention group received haloperidol in four studies (9, 10, 23, 24) in 5 mg doses, to a maximum of 15–30 mg total daily. Two studies (23, 25) used quetiapine as their study drug, to a maximum of 200–300 mg daily. Finally, one study (24) examined ziprasidone, using 5 mg to a maximum of 40 mg total daily dose. In the studies that reported it (9, 24), median treatment duration was 3–4 days.

Risk of Bias

All five studies (9, 10, 23–25) were deemed to have a low ROB in all domains for all outcomes (see **Supplement Table 5**, http://links.lww.com/CCM/H511, for full justification). All studies were double-blind and had acceptable allocation methods. Outcome data were available for all participants for all outcomes of interest and an appropriate tool was used to measure the outcomes of interest. Finally, all five studies reported results and conducted their analyses in accordance with prespecified plans.

Delirium- and Coma-Free Days

Four studies (9, 10, 23, 24) enrolling a total of 1691 patients reported delirium- and coma-free days. The use of antipsychotics did not result in a difference in delirium-/coma-free days (MD 0.90 d; 95% CI, –0.32 to 2.12; moderate certainty) (**Fig. 2**). A subgroup analysis of studies by typical versus atypical antipsychotics and another by publication year did not identify any subgroup interaction (**Supplement Figs 1** and **2**, http://links.lww.com/CCM/H511). There were insufficient reported data to complete subgroup analyses by hyperactive versus hypoactive delirium or comparator agent.

Mortality

Four studies (9, 10, 23, 24) for a total of 1714 patients captured 28-day mortality. Antipsychotic medications resulted in no difference in 28-day mortality in patients with delirium (RR 0.87; 95% CI, 0.75–1.01; moderate certainty) (**Supplement Fig. 3**, http://links.lww.com/CCM/H511). Subgroup analyses by typical versus atypical antipsychotic did not reveal any subgroup interaction, nor by publication year (**Supplement Figs 4** and **5**, http://links.lww.com/CCM/H511). Analysis by delirium type or comparator agent could not be completed due to insufficient published data.

Pooled analysis of five studies (9, 10, 23–25) (n = 1750) revealed no difference in mortality at longest follow-up with the use of antipsychotics (RR 0.89; 95% CI, 0.79–1.01; moderate certainty) (**Fig. 3*A***). Subgroup analyses by type of antipsychotic and year of publication also did not identify any subgroup effects (**Supplement Figs 6** and **7**, http://links.lww.com/CCM/H511). Furthermore, subgroup analysis by length of longest mortality assessment did not identify a mortality response (**Supplement Fig. 8**, http://links.lww.com/CCM/H511). Further preplanned subgroup analyses could not be completed due to lack of data.

Duration of Mechanical Ventilation

Five studies (9, 10, 23–25) (n = 1750) reported duration of mechanical ventilation. Antipsychotic therapy

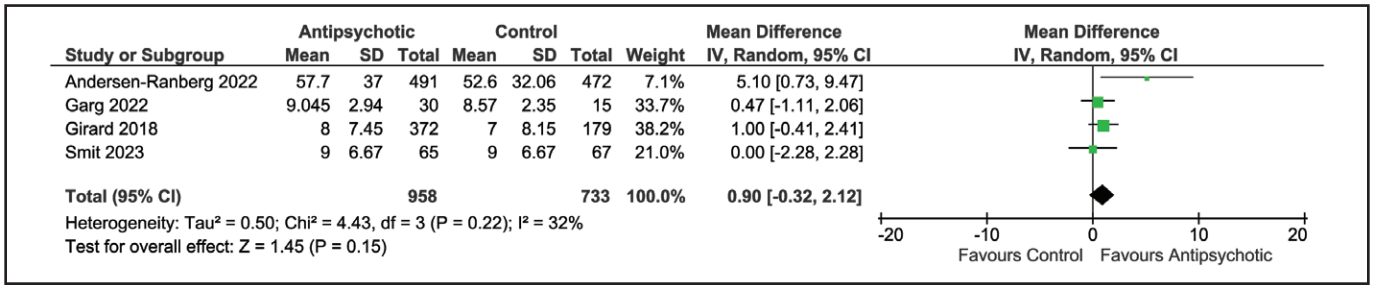
Antipsychotic
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Andersen-Ranberg 2022 57.7 37 491 52.6 32.06 472 7.1% 5.10 [0.73, 9.47]
Garg 2022 9.045 2.94 30 8.57 2.35 15 33.7% 0.47 [-1.11, 2.06]
Girard 2018 8 7.45 372 7 8.15 179 38.2% 1.00 [-0.41, 2.41]
Smit 2023 9 6.67 65 9 6.67 67 21.0% 0.00 [-2.28, 2.28]
Total (95% CI) 958 733 100.0% 0.90 [-0.32, 2.12]
Heterogeneity: Tau² = 0.50; Chi² = 4.43, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 1.45 (P = 0.15)
-20
-10
0
10
20
Favours Control
Favours Antipsychotic

Figure 2. *Forest plot* showing delirium-free days. IV = inverse variance, df = degrees of freedom.

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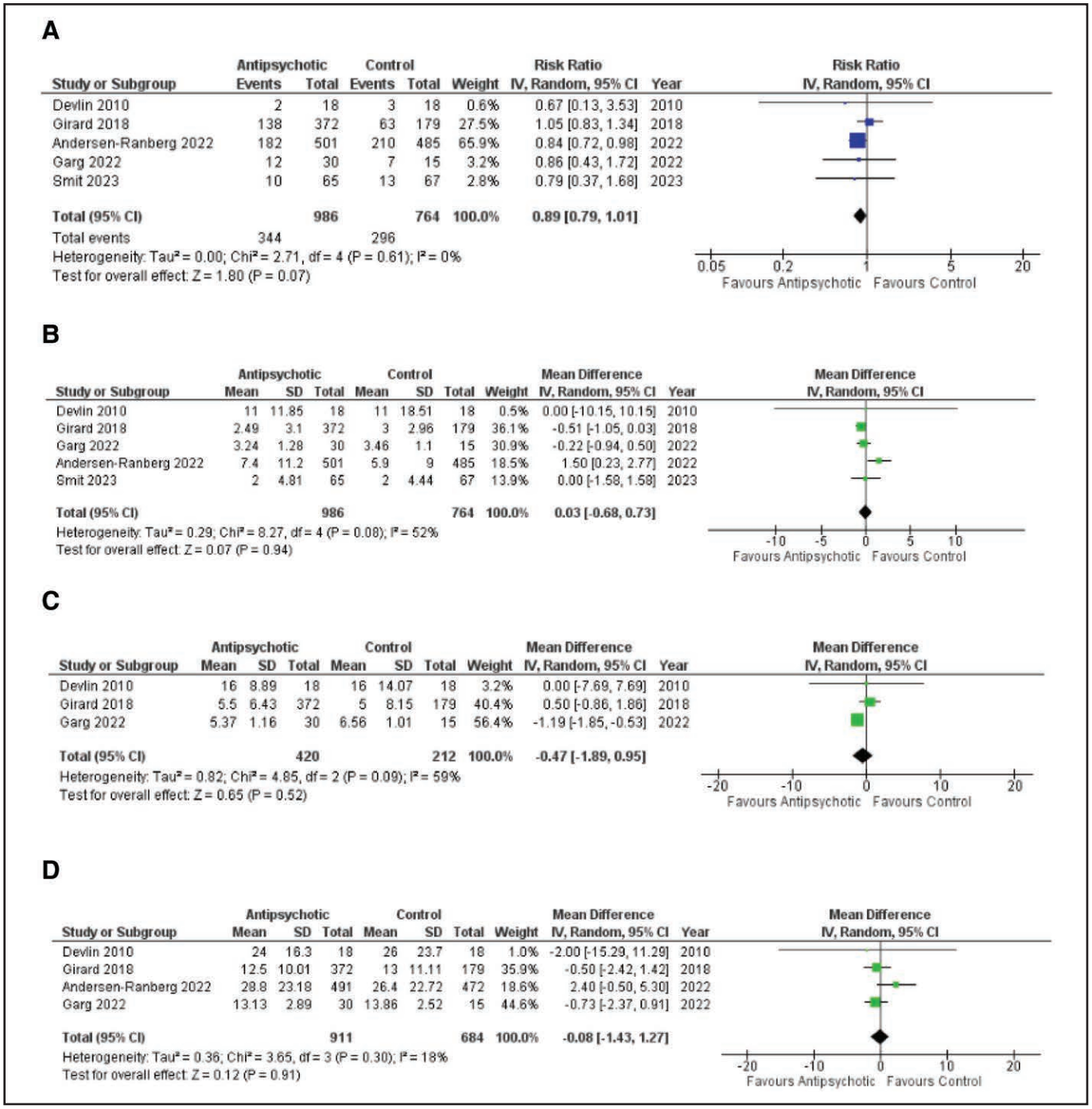
A
Antipsychotic
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Devlin 2010 2 18 3 18 0.6% 0.67 [0.13, 3.53] 2010
Girard 2018 138 372 63 179 27.5% 1.05 [0.83, 1.34] 2018
Andersen-Ranberg 2022 182 501 210 485 65.9% 0.84 [0.72, 0.98] 2022
Garg 2022 12 30 7 15 3.2% 0.86 [0.43, 1.72] 2022
Smit 2023 10 65 13 67 2.8% 0.79 [0.37, 1.68] 2023
Total (95% CI) 986 764 100.0% 0.89 [0.79, 1.01]
Total events 344 296
Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
0.05 0.2 1 5 20
Favours Antipsychotic Favours Control
B
Antipsychotic
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Devlin 2010 11 11.85 18 11 18.51 18 0.5% 0.00 [-10.15, 10.15] 2010
Girard 2018 2.49 3.1 372 3 2.96 179 36.1% -0.51 [-1.05, 0.03] 2018
Garg 2022 3.24 1.28 30 3.46 1.1 15 30.9% -0.22 [-0.94, 0.50] 2022
Andersen-Ranberg 2022 7.4 11.2 501 5.9 9 485 18.5% 1.50 [0.23, 2.77] 2022
Smit 2023 2 4.81 65 2 4.44 67 13.9% 0.00 [-1.58, 1.58] 2023
Total (95% CI) 986 764 100.0% 0.03 [-0.68, 0.73]
Heterogeneity: Tau² = 0.29; Chi² = 8.27, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 0.07 (P = 0.94)
-10 -5 0 5 10
Favours Antipsychotic Favours Control
C
Antipsychotic
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Devlin 2010 16 8.89 18 16 14.07 18 3.2% 0.00 [-7.69, 7.69] 2010
Girard 2018 5.5 6.43 372 5 8.15 179 40.4% 0.50 [-0.86, 1.86] 2018
Garg 2022 5.37 1.16 30 6.56 1.01 15 56.4% -1.19 [-1.85, -0.53] 2022
Total (95% CI) 420 212 100.0% -0.47 [-1.89, 0.95]
Heterogeneity: Tau² = 0.82; Chi² = 4.85, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.65 (P = 0.52)
-20 -10 0 10 20
Favours Antipsychotic Favours Control
D
Antipsychotic
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Devlin 2010 24 16.3 18 26 23.7 18 1.0% -2.00 [-15.29, 11.29] 2010
Girard 2018 12.5 10.01 372 13 11.11 179 35.9% -0.50 [-2.42, 1.42] 2018
Andersen-Ranberg 2022 28.8 23.18 491 26.4 22.72 472 18.6% 2.40 [-0.50, 5.30] 2022
Garg 2022 13.13 2.89 30 13.86 2.52 15 44.6% -0.73 [-2.37, 0.91] 2022
Total (95% CI) 911 684 100.0% -0.08 [-1.43, 1.27]
Heterogeneity: Tau² = 0.36; Chi² = 3.65, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.12 (P = 0.91)
-20 -10 0 10 20
Favours Antipsychotic Favours Control

Figure 3. *Forest plots* showing mortality at longest follow-up (**A**), duration of mechanical ventilation (d) (**B**), ICU length of stay (d) (**C**), and hospital length of stay (d) (**D**). IV = inverse variance, *df* = degrees of freedom.

did not impact the duration of mechanical ventilation (MD 0.03 d; 95% CI, –0.68 to 0.73; moderate certainty) (**Fig. 3*B***). No subgroup interaction by typical versus atypical antipsychotics was identified, nor in studies conducted before and after 2018 (**Supplement Figs 9** and **10**, http://links.lww.com/CCM/H511) and further analyses by type of delirium and comparator agent could not be performed.

ICU Length of Stay

Pooled analysis of three studies (23–25) (n = 632) revealed no difference in ICU length of stay with the administration of antipsychotics (MD –0.47 d; 95% CI, –1.89 to 0.95; moderate certainty) (**Fig. 3*C***). Subgroup analyses by class of antipsychotic and publication year failed to identify any subgroup interaction

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(**Supplement Figs 11** and **12**, http://links.lww.com/CCM/H511). Subgroup analyses by type of delirium and comparator agent were not performed due to a lack of data.

Hospital Length of Stay

Four studies (9, 23–25) reported hospital length of stay for a total of 1595 participants. Treatment with antipsychotic medications did not decrease length of stay (MD −0.08 d; 95% CI, −1.43 to 1.27; high certainty) (**Fig. 3*D***). There were no identified subgroup interactions by class of antipsychotic or publication year (**Supplement Figs 13** and **14**, http://links.lww.com/CCM/H511). Finally, analysis by type of delirium and comparator agent was not able to be performed.

Adverse Events

Three studies (9, 10, 24) (n = 1679) reported adverse events, including neuroleptic malignant syndrome, Torsades de Pointes, prolonged QT, and extrapyramidal side effects. Overall, the use of antipsychotic medications did not result in an increase in adverse events (RR 1.27; 95% CI, 0.71–2.30; high certainty) (**Fig. 4**). A subgroup analysis examining typical versus atypical antipsychotics failed to identify any significant subgroup difference nor did another by publication year (**Supplement Figs 15** and **16**, http://links.lww.com/CCM/H511). Delirium type and comparator agent could not be examined due to a paucity of data.

Cognitive Function/General Disability Score, Disposition Destination, and Use of Rescue Medications

None of cognitive function, disposition destination, or use of rescue medications could be meta-analyzed due to a lack of reported data.

Meta-Regression, Sensitivity Analysis, and Trial Sequential Analysis

Due to the inadequate number of eligible studies, meta-regression could not be performed.

Sensitivity analysis excluding studies with high or some concern for risk or bias was not conducted as all included studies were deemed to have low ROB. Planned sensitivity analysis excluding abstracts was also not conducted as all included studies were published in full-text form.

The TSA was inconclusive for all outcomes examined (delirium-free days and mortality) as they did not meet the required information size and boundaries for benefit, harm, or futility were not crossed (**Supplement Figs 17** and **18**, http://links.lww.com/CCM/H511).

DISCUSSION

In this systematic review and meta-analysis, we included five studies (9, 10, 23–25) (n = 1750) comparing the use of antipsychotic medications to usual care or placebo in critically ill adult patients with delirium. Overall, we found no difference in delirium- or coma-free days (moderate certainty), mortality (moderate certainty), duration of mechanical ventilation (moderate certainty), ICU length of stay (moderate certainty), hospital length of stay (high certainty), or adverse events (high certainty). Subgroup analysis by class of antipsychotic medication (typical vs. atypical) did not identify any interaction for any of these outcomes, nor did analysis by publication year.

Although previous systematic reviews have been completed on this question, they vary from ours in several ways. A recent review (26), which also captured the results of the AID-ICU trial included all critically ill patients irrespective of presence of delirium, and therefore did not examine the true impact of antipsychotics

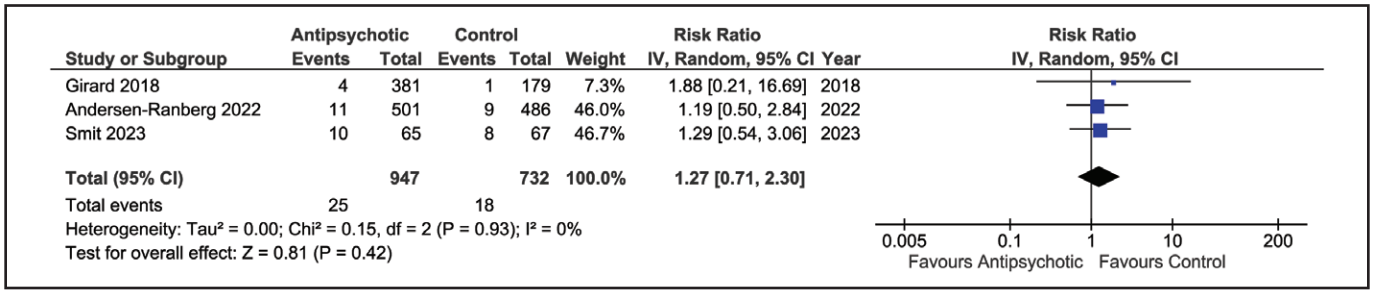
Antipsychotic
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Girard 2018 4 381 1 179 7.3% 1.88 [0.21, 16.69] 2018
Andersen-Ranberg 2022 11 501 9 486 46.0% 1.19 [0.50, 2.84] 2022
Smit 2023 10 65 8 67 46.7% 1.29 [0.54, 3.06] 2023
Total (95% CI) 947 732 100.0% 1.27 [0.71, 2.30]
Total events 25 18
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
0.005
0.1
1
10
200
Favours Antipsychotic
Favours Control

Figure 4. *Forest plot* showing risk of adverse events. IV = inverse variance, df = degrees of freedom.

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exclusively as a treatment modality. Another recent review (8) included the EuRIDICE study; however, its included interventions and assessed outcomes vary significantly from ours. Where we examined antipsychotic medications as a class, the review by Andersen-Ranberg et al examined haloperidol specifically as an intervention and had a very heterogenous inclusion of comparators including other antipsychotics, benzodiazepines, dexmedetomidine, opioids, and antiemetics. Furthermore, although they were able to analyze and report on mortality for the subgroup of trials with placebo as comparator and ultimately identified the same mortality estimate, their analysis of serious adverse events was interesting in its inclusion of mortality among this group of events, where we chose to analyze adverse events as an independent entity. Despite this difference, both reviews ultimately identified no increase in adverse events. Furthermore, with this review we present expanded results that include duration of mechanical ventilation, ICU, and hospital length of stay, which were not captured in the other recent meta-analysis. Finally, a third recent review (6) was less restrictive in its judgment of which trials constituted a critically ill population and most others have examined specific antipsychotic medications (27) rather than their use as a class. Despite these differences, our findings are consistent with prior reviews in that there was no observed difference in mortality or duration of delirium. It is again interesting to note that despite its concerns for harm, the evidence thus far, now corroborated by two systematic reviews, has not demonstrated a significant increase in (short term) adverse events with the use of antipsychotics despite reasonably high doses. This may be of particular interest in the hyperactive subset of patients for whom agents with sedating properties are necessary for safety and to facilitate care. Of note, the most recent guideline (3) to provide direction on the management of delirious critically ill patients was published before our systematic review and numerous recent studies we identified, and as such an update could be considered to reexamine clinical practice guidance on antipsychotic administration in this population.

There are multiple strengths to this review. We undertook a methodologically rigorous process and adhered to an a priori registered protocol. An extensive search of the literature was performed, and all aspects of the review were duplicated. Finally, the addition of TSA added strength to our findings and further supported the need for ongoing large-scale studies on this subject.

Our review does, however, have limitations. The reported data regarding usage of rescue medications could not be combined for a meta-analysis, and thus we could not assess the rate of use of open-label antipsychotics and total dose received in each arm. A high rate of open-label antipsychotic use in the control arms may have resulted in a falsely negative result where a true benefit may in fact exist.

It is notable that the majority of patients (67%) had hypoactive rather than hyperactive delirium at the time of randomization; however, lack of reported data did not make it possible to assess for subgroup differences in these populations. This analysis, even if possible, would have been further limited by the challenges of elucidating sedative medications versus hypoactive delirium, as well as categorizing patients who fluctuate across the spectrum of hypoactivity and hyperactivity. As previously mentioned, exploring the risk and benefit profile in patients who have agitated delirium and require chemical restraint may contribute valuable practice-changing knowledge. Additionally, the information available in the published studies did not allow us to assess whether the administration of antipsychotic medications has a different impact on patients with incident versus prevalent delirium (28). It is certainly possible that patients admitted to ICU who had delirium prior would experience a greater delay to medication exposure than those who developed delirium during ICU admission and thus experience less potential benefit, and this presents another important area of future study.

Furthermore, although we identified no difference in short-term adverse events, the available data did not allow for analysis of adverse events that may occur on a longer scale, particularly if antipsychotics are continued after hospital discharge. This is notable as evidence supports that approximately 20% of patients with delirium in hospital are discharged home with ongoing antipsychotics (29) and the consequences of this phenomenon are unclear.

The small participant numbers in many trials and the fact that subgroups are likely to be underpowered are cause for further uncertainty, although subgroup results should only be considered hypothesis generating regardless. Finally, although the initial intent was

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to report delirium-free days as the primary outcome, the primary outcome was changed from "delirium-free days" to "delirium- and coma-free days" during the completion of the systematic review given delirium and coma are distinct clinical sequelae of acute encephalopathy and delirium cannot be evaluated in unresponsive patients (30).

CONCLUSIONS

In conclusion, our systematic review and meta-analysis demonstrated with moderate certainty evidence that there is no difference in delirium- or coma-free days when antipsychotic medications are administered to critically ill patients with delirium. Future studies examining the role of antipsychotics on delirium symptoms and sequelae (e.g., falls, disrupted sleep, and dementia), not evaluated in current RCTs, are required.

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